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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER

KAM, CHIH MIN

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PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No. 10/563,536	Applicant(s) WIDMANN ET AL.	
	Examiner CHIH-MIN KAM	Art Unit 1656	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 26 May 2009.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-9, 11, 12, 14, 15, 17-19, 23, 25 and 27-39 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1-9, 11, 12, 14, 15, 17-19, 23, 25 and 27-39 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☒ The specification is objected to by the Examiner.
- 10) ☒ The drawing(s) filed on 28 December 2005 is/are: a) ☒ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- * See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413) |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | Paper No(s)/Mail Date. _____ |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08) | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| Paper No(s)/Mail Date <u>12/28/05;6/11/09</u> . | 6) <input type="checkbox"/> Other: _____ |

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DETAILED ACTION

Election/Restrictions

1. Applicant's election with traverse of SEQ ID NO:4 and alkylating agent as the elected species, in the response to restriction requirement filed May 26, 2009 is acknowledged. The traversal is on the ground(s) that the Examiner has presented no reasoned basis as to why the species lack unity of invention and/or why the species are not linked as to form a single invention concept under PCT Rule 13. Applicants' response has been considered and found persuasive. Thus, the requirement for species election is withdrawn, and claims 1-9, 11, 12, 14, 15, 17-19, 23, 25 and 27-39 are examined.

Abstract

2. The abstract of the disclosure is objected to because it recites the legal phraseology "said peptide", which should be avoided. Correction is required. See MPEP § 608.01(b).

Claim Objections

3. Claims 1-3, 31, 33, 34, 38 and 40-41 objected to because the claim recites amino acid sequences without providing the sequence identifier "SEQ ID NO:", or recites, for example, "SEQ ID No. 1", which should be "SEQ ID NO:1". Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

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4. Claims 1-9, 11, 12, 14, 15, 17-19, 23, 25 and 27-39 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a pharmaceutical composition comprising: i) at least one peptide which is shorter than the N2 sequence of the RasGAP protein and comprises the amino acid sequence WXWVTXXRTX, wherein X represents an amino acid, and ii) and a specific genotoxin such as cisplatin, adriamycin and mitoxantrone, wherein the at least one peptide enhances the ability of said genotoxin to kill selectively cancer cells; a kit for treating cancer comprising the pharmaceutical composition; and a method for enhancing apoptosis in a cancer cell, a method for selectively killing cancer cells; or a method for treating cancer in a subject using the pharmaceutical composition; and the use of a pharmaceutical composition shown in the prior art, does not reasonably provide enablement for a pharmaceutical composition comprising: i) at least one peptide which is shorter than the N2 sequence of the RasGAP protein and comprises the amino acid sequence WXWVTXXRTX, or variants thereof, wherein X represents an amino acid, and ii) and a genotoxin, wherein said at least one peptide enhances the ability of said genotoxin to kill selectively cancer cells; a kit for treating or preventing cancer comprising the pharmaceutical composition; and a method for enhancing apoptosis in a cancer cell, a method for selectively killing cancer cells; or a method for treating or preventing cancer in a subject using the pharmaceutical composition, wherein the peptide variant and the genotoxin are not defined. The specification does not enable a person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

Claims 1-9, 11, 12, 14, 15, 17-19, 23, 25 and 27-39 are directed to a pharmaceutical composition comprising a N2 fragment of the RasGAP protein comprising the amino acid

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sequence WXWVTXXRTX, or variants thereof, and a genotoxin; a kit for treating or preventing cancer comprising the pharmaceutical composition; and a method for enhancing apoptosis in a cancer cell, for selectively killing cancer cells, or for treating or preventing cancer in a subject using the pharmaceutical composition. The specification, however, only discloses cursory conclusions (page 3, line 29-page 4, line 7), which state the invention provides a peptide consisting essentially of the N2 sequence of the RasGAP protein, a fragment thereof or a variant thereof, which enhances the ability of a drug to kill selectively cancers cells, and a pharmaceutical composition comprising the peptide. The present application does not provide sufficient teaching/guidance as to enable the full scope of the claims. The factors considered in determining whether undue experimentation is required, are summarized in In re Wands (858 F2d at 731,737, 8 USPQ2d at 1400,1404 (Fed. Cir.1988)). The factors most relevant to this rejection are the breadth of the claims, the absence or presence of working examples, the state of the prior art and relative skill of those in the art, the predictability or unpredictability of the art, the nature of the art, the amount of direction or guidance presented, and the amount of experimentation necessary.

(1). The breadth of the claims:

The breadth of the claim is broad and encompasses unspecified variants regarding the peptide variants of N fragment of RasGAP and genotoxins in the pharmaceutical composition, and the use of the composition in the method of preventing cancers, which are not adequately described or demonstrated in the specification.

(2). The absence or presence of working examples:

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While Example 2 discloses specific RasGAP N2 fragment potentiates the apoptotic response of tumor cells induced by specific genotoxins such as cisplatin, adriamycin and mitoxantrone (Figs. 1, 2 and 4), the specification does not sufficiently describe the use and effect of peptide variant in enhancing various genotoxins and a method of preventing cancers using a pharmaceutical composition comprising a RasGAP N2 fragment and a genotoxin.

(3). The state of the prior art and relative skill of those in the art:

The art (e.g., Yang *et al.*, Mol. And Cell. Biology 21, 5346-5358 (2001)) teach N1 and N2 fragments of RasGAP sensitizes HeLa cells (a tumor cell) toward DNA induced apoptosis in the presence and absence of cisplatin at various concentrations (see paragraph 10 below). However, the general knowledge and level of the skill in the art do not supplement the omitted description, the specification needs to provide specific guidance on the structures of active peptide variants and their use in the method of treating or preventing cancers to be considered enabling for variants.

(4). Predictability or unpredictability of the art:

The claims encompass the use variants of N2 fragment of the RasGAP protein in the method of treating or preventing cancers, however, the specification does not provide sufficient teachings in the structures of peptide variants and their use in the method of treating or preventing cancers. Furthermore, the specification does not show how the cancer can be prevented by the composition comprising the N2 peptide, for example, if the cancer does not occur (prevention), how to determine the effect of the composition. Thus, the structures and effects of N2 peptide variants are not predictable.

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(5). The amount of direction or guidance presented and the quantity of experimentation necessary:

The claims are directed to a pharmaceutical composition comprising a N2 fragment of the RasGAP protein comprising the amino acid sequence WXWVTXXRTX, or variants thereof, and a genotoxin; a kit for treating or preventing cancer comprising the pharmaceutical composition; and a method for enhancing apoptosis in a cancer cell, for selectively killing cancer cells, or for treating or preventing cancer in a subject using the pharmaceutical composition.

While the specification discloses specific RasGAP N2 fragment enhances the apoptotic response of tumor cells induced by cisplatin, adriamycin and mitoxantrone (Example 2), the specification does not sufficiently describe the use and effect of peptide variants in enhancing various genotoxins and a method of preventing cancers using a pharmaceutical composition comprising a RasGAP N2 fragment and a genotoxin. Furthermore, the specification does not teach how to prevent cancers using the pharmaceutical composition comprising a RasGAP N2 fragment and a genotoxin. Since the specification does not provide sufficient teachings on the structures and effects of active N2 fragment variants, it is necessary to carry out undue experimentation to identify an active N2 fragment variants and to assess its effect in treating or preventing cancers.

(6). Nature of the Invention

The scope of the claim includes a pharmaceutical composition comprising a N2 fragment variant of the RasGAP protein and a genotoxin; and a method for treating or preventing cancer in a subject using the pharmaceutical composition, but the specification does not provide sufficient teachings on the use and effect of active N2 fragment variants in treating or preventing cancers. Thus, the disclosure is not enabling for the reasons discussed above.

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In summary, the scope of the claim is broad, the working example does not demonstrate the claimed methods associated with variants, the structure and the effect of N2 fragment variant is not predictable, and the teachings in the specification are limited, therefore, it is necessary to carry out undue experimentation to identify an active N2 fragment variants and to assess its effect in treating or preventing cancers.

5. Claims 1-9, 11, 12, 14, 15, 17-19, 23, 25 and 27-39 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 1-9, 11, 12, 14, 15, 17-19, 23, 25 and 27-39 are directed to a pharmaceutical composition comprising: i) at least one peptide which is shorter than the N2 sequence of the RasGAP protein and comprises the amino acid sequence WXWVTXXRTX, or variants thereof, wherein X represents an amino acid, and ii) and a genotoxin, wherein said at least one peptide enhances the ability of said genotoxin to kill selectively cancer cells; a kit for treating or preventing cancer comprising the pharmaceutical composition; and a method for enhancing apoptosis in a cancer cell, a method for selectively killing cancer cells; or a method for treating or preventing cancer in a subject using the pharmaceutical composition.

In *University of California v. Eli Lilly & Co.*, 43 USPQ2d 1938, the Court of Appeals for the Federal Circuit has held that "A written description of an invention involving a chemical genus, like a description of a chemical species, 'requires a precise definition, such as by structure, formula, [or] chemical name,' of the claimed subject matter sufficient to distinguish it from other

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materials". As indicated in MPEP § 2163, the written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice, reduction to drawings, or by disclosure of relevant, identifying characteristics, i.e., structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show that Applicant was in possession of the claimed genus. In addition, MPEP § 2163 states that a representative number of species means that the species which are adequately described are representative of the entire genus. Thus, when there is substantial variation within the genus, one must describe a sufficient variety of species to reflect the variation within the genus.

While the specification discloses characterization of N2 fragment of RasGAP (residues 158-455), specific fragments containing SH3 domain (residues 284-341) and containing residues 317-326 (SEQ ID NO:4 and 14), which enhances apoptosis of tumor cells in the presence of cisplatin, adriamycin or mitoxantrone (Figs. 1, 2 and 4; Example 2), the specification does not disclose a genus of peptide variants which are shorter than the N2 sequence (298 residues) of the RasGAP protein and comprises the amino acid sequence WXWVTXXRTX that enhance the ability of any genotoxin to kill cancer cells in pharmaceutical compositions comprising the peptide and a genotoxin. Some specific fragments of N2 fragment of RasGAP that enhances apoptosis of specific genotoxins such as cisplatin, adriamycin and mitoxantrone (Figs. 1, 2 and 4; Example 2) does not provide sufficient written description for the whole genus of pharmaceutical compositions comprising different peptide variants and genotoxins, which would have substantial variation within the whole genus of pharmaceutical compositions comprising

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numerous combinations. The lack description on the combination of peptide variants and various genotoxins, and the lack of representative species as encompassed by the claims, applicants have failed to sufficiently describe the claimed invention, in such full, clear, concise terms that a skilled artisan would not recognize applicants were in possession of the claimed invention.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

6. Claims 9, 12, 23, 27, 28, 33-38 and 40-43 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.
7. Claim 9 is indefinite because the claim recites the term, for example, HAV-TAT₄₈₋₅₇ peptide, without providing a reference sequence with sequence identifier “SEQ ID NO:”, it is not clear what sequence the residues 48-78 refer to.
8. Claim 12 is indefinite because of the use of the term “other platinum derivatives”. The term cited renders the claim indefinite, it is not what structures the derivatives have, and how different the derivatives are from the parent compound. Use of the term “other platinum compounds” is suggested.
9. Claims 23, 27, 28, 33-38 and 40-43 are indefinite because the claims lack an essential step in the claimed methods. The missing step is an effective amount used in the method. Claims

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23, 27, 28, 34-36, 38 and 41-43 are included in this rejection for being dependent on a rejected claim and not correcting the deficiency of the claim from which they depend.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

10. Claims 1-3, 11, 12, 27, 28 and 33-39 are rejected under 35 U.S.C. 102(b) as anticipated by Yang *et al.* (Mol. And Cell. Biology 21, 5346-5358 (2001); reference C4 in the IDS filed December 28, 2005) as evidenced by Widmann *et al.* (US 20060234929).

Yan *et al.* teach characterization of RasGAP and its N-fragment (residues 1-455), where N-fragment contain N1 fragment (residues 1-157) and N2 fragment (residues 158-455), which contains 2 SH2 and one SH3 domain (Fig.1; page 5348, right column), and SH3 contains WXWVTXXRTX or SEQ ID NO:4 (WMWVTNLRTD) as evidenced by Widmann *et al.* (paragraphs [0069],[0070]; Tables 1 and 2). The reference also teaches N1 and N2 fragments of RasGAP sensitizes HeLa cells (a tumor cell) toward DNA induced apoptosis, where HeLa cells were transfected with plasmid encoding HA-GAP caspase cleavage fragments (i.e., N1 and N2 fragments), and the cells were treated in the presence and absence of cisplatin at various concentrations, it was found that the N fragment, N1 and N2 fragments enhances apoptosis of HeLa cells in the presence of cisplatin (page 5351, left column-page 5352, left column; page 5354; Figs. 7 and 8; claims 1-3, 11, 12, 27, 28 and 33-39).

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Conclusion

11. No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Chih-Min Kam whose telephone number is (571) 272-0948. The examiner can normally be reached on 8.00-4:30, Mon-Fri.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Andrew Wang can be reached at 571-272-0811. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/Chih-Min Kam/

Primary Examiner, Art Unit 1656

CMK

July 18, 2009